EDITORIAL
DOI: 10.3904/kjim.2011.26.2.132

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The Endoscopic Cryotherapy of Lung and Bronchial Tumors: A Systematic Review - Can We Expect a New Era of Cryotherapy in Lung Cancer?

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See Article on Page 137-144

Since the introduction of the flexible bronchoscope by Ikeda et al. [1], it has become one of the most important tools for diagnosing and treating pulmonary diseases. Its applications range from airway evaluations to interventional therapy for airway lesions. Interventional bronchoscopy using rigid and flexible bronchoscopes has progressed with the introduction of new techniques to relieve airway obstructions and bleeding control, which can be life-threatening complications of advanced lung cancer. Malignancy in the central airway may cause diverse clinical signs and symptoms depending on the location, growth rate of the obstructive lesion, diagnosis time, and involvement of surrounding structures [2,3]. The efficacy of interventional bronchoscopy for palliation of central airway obstructions has been well established, and its curative potential for early lung cancer has evolved along with current treatment modalities. The main indication for therapeutic bronchoscopy is the presence of an airway disorder resulting in a central airway obstruction to relief blockage [4]. Interventional bronchoscopy, particularly therapeutic bronchoscopy, includes many diverse modalities, such as the Nd:YAG laser, electrocautery, argon plasma coagulation, photodynamic therapy, airway stenting, brachytherapy, and cryotherapy, which all have advantages and disadvantages.

Endobronchial cryotherapy, which is intended to ablate endobronchial tumors and carcinomas in situ using an ice freezing effect, was initially reported in the 1970s [5]. Although it was largely abandoned in favor of other modalities, such as laser treatment, particularly in the United States, interest in cryotherapy has continued in Europe. Endobronchial cryotherapy has been used to destroy endobronchial tumors by its cytotoxic effects of freezing tissue, thus, causing tissue death. Its clinical uses are primarily in treating patients with inoperable obstructive central lung cancers. The mechanism of local tissue destruction is applying extremely low temperatures (below -20 to -40°C). The first successful use of low temperature for treating a tumor was reported by James Arnott [6] to treat an advanced uterine carcinoma more than 150 years ago. Rigid and semi-rigid cryoprobes are used with a rigid bronchoscope, whereas a flexible cryoprobe can be used with both instruments. Cryotherapy has also been used to treat carcinoma in situ as well as benign endobronchial tumors. The advantage of endobronchial cryotherapy is that it has proven effective with minimal complications. It is also relatively easy to use and economical compared with other therapeutic modalities. Cryotherapy is safe, with no danger of bronchial wall perforation, no radiation danger, no risk of electrical accidents or fires, and does not require much special training. Patients tolerate the procedure well and show a significant improvement in symptoms. Disadvantages include delayed results and the requirement

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for multiple bronchoscopies to remove debris or to retreat, which is a serious issue for cryotherapy in a patient with impending respiratory failure due to an obstructive airway lesion. The success of freeze injury, which is the main mechanism of cryotherapy for malignancy, may be influenced by many factors; the survival of cells is dependent on the cooling rate [7,8], the thawing rate [9], the lowest temperature achieved [10], and repeated freeze-thaw cycles [11]. Applying a low-temperature probe to a tissue first induces immediate adherence between the probe and tissue and then the appearance of intra- and extracellular ice crystals [12]. These crystals damage intracellular organelles, particularly mitochondria. The formation of pure extracellular ice crystals causes additional ion and water movement, resulting in cellular dehydration. A maximum effect is achieved by rapid cooling of the tissue followed by slow thawing [13].

As evidence for additional cryotherapy applications for endobronchial tumors increase for patients with advanced lung cancer who suffer from obstructive lesions, Lee and colleagues provide a systematic innovative literature review of cryotherapy in this issue of KJIM (see page 137-144). This group systematically analyzed and evaluated the endoscopic cryotherapy literature and present reference materials useful for treating endobronchial airway obstruction by tumors. Sixteen key studies were used to determine the safety and effectiveness of cryotherapy. Based on this study, the overall success rate for effective recanalization of tumor obstruction was about 80%, and the complication rate of the cryotherapy procedure was 0-11.1% of the cases, most of which were minor and manageable with conservative methods. Some studies evaluated for this systemic review revealed much improvement in respiratory symptoms, pulmonary function tests, and performance status even with the limitations of the study data. This review also showed a 0-7.1% mortality rate within 30 days of the procedure in five of 16 studies. The case study by Hetzel et al. [14] had a 61% complete response rate and a 22% partial response rate, which is as effective as other interventional modalities. This study also shows that most of the cases resulted in airway reopening and endobronchial tumor shrinkage, suggesting that cryotherapy can still be used almost exclusively for palliation and not for curative intent in advanced lung cancers with the advantage of ease of use and minimal complications. Even after a systemic literature review, there are some limitations to this study; the clinical efficacy and complications of cryotherapy cannot be readily compared considering the diverse clinical situations, many differing indications, and different methods for successful evaluation. Furthermore, the use of other co-modalities, such as combined laser or electrocautery treatment, must be considered.

Advanced stage lung cancer poses a serious threat to quality of life due to local tumor growth and distant metastases. Most patients suffer from end-stage tumor recurrences and failed treatments, including surgery or chemoradiotherapy. Imminent suffocation and poor physical condition may provide little space for a timely and safe intervention. Interventional bronchoscopy, including cryotherapy, is warranted and should be considered for palliation of obstructive lesions.

Although cryotherapy is a unique destructive method based on the cytotoxic effects of cold on living tissue, the role of cryotherapy is still limited compared with other endobronchial treatments. It is safe, less expensive, and easy to use, but less versatile than electrocautery and has a delayed effect. Therapeutic bronchoscopy, including cryotherapy, may be of benefit for patients requiring chemotherapy, including recent target agents for epidermal growth factor mutation, echinoderm microtubule-associated protein-like 4, and anaplastic lymphoma kinase or irradiation therapy. Further investigations in this area may lead to an additional new therapeutic modality for advanced lung cancer. Can we expect a new era of cryotherapy for lung cancer soon? **(Korean J Intern Med 2011;26:132-134)**

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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